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Antimicrobial Susceptibility of *Pseudomonas aeruginosa* to Ceftazidime-Avibactam, Ceftolozane-Tazobactam, Piperacillin-Tazobactam, and Meropenem Stratified by U.S. Census Divisions: Results from the 2017 INFORM Program

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ABSTRACT *Pseudomonas aeruginosa* isolates (n = 1,909) were collected from 70 U.S. medical centers, and their susceptibilities were tested using the broth microdilution method. Ceftazidime-avibactam (MIC_{50}/MIC_{90}, 2/8 mg/liter) and ceftolozane-tazobactam (MIC_{50}/MIC_{90}, 0.5/2 mg/liter) were the most active (i.e., had the highest susceptibility rates) compounds after colistin, with national susceptibility rates of 96.9% and 97.5%, respectively. Overall, piperacillin-tazobactam (MIC_{50}/MIC_{90}, 4/128 mg/liter) and meropenem (MIC_{50}/MIC_{90}, 0.5/16 mg/liter) were active against 77.5% and 76.0% of the isolates, respectively. Susceptibility variations across census divisions were documented for many antimicrobials.

KEYWORDS *Pseudomonas aeruginosa*, antimicrobial resistance, β-lactamases, inhibitor combinations

Pseudomonas aeruginosa bacteria are a major cause of nosocomial infections worldwide, including sepsis, hospital-acquired pneumonia, ventilator-associated pneumonia (VAP), skin and skin structure infections (SSSIs), and urinary tract infections (UTIs) (1). The increasing prevalence of multidrug-resistant (MDR) and extensively drug-resistant (XDR) strains of *P. aeruginosa* is a cause of great concern, and the selection of appropriate empirical and definitive antimicrobial treatments may be problematic in medical centers with elevated resistance rates (2).

Ceftazidime-avibactam and ceftolozane-tazobactam are the most recently U.S. FDA-approved cephalosporin–β-lactamase inhibitor combinations for treating infections caused by Gram-negative bacilli, including *P. aeruginosa* (3–6). Both combinations have demonstrated potent *in vitro* activity and good coverage against *P. aeruginosa* (7, 8); however, a limited number of studies compare the *in vitro* activities of these two compounds against large collections of randomly selected clinical isolates (9). In the present study, we evaluated the *in vitro* activities of ceftazidime-avibactam, ceftolozane-tazobactam, and many comparator agents against a large collection of recent clinical *P. aeruginosa* isolates from U.S. medical centers.

A total of 1,909 *P. aeruginosa* isolates (1 per infection episode) were consecutively collected from 70 U.S. medical centers (35 states from all 9 census divisions) in 2017 as part of the INFORM program. Only bacterial isolates determined to be significant by local criteria as the reported probable cause of an infection were included in this investigation, and the results were stratified by U.S. census division. Species identification was confirmed, when necessary, by matrix-assisted laser desorption ionization–time of flight mass spectrometry using the Bruker Daltonics MALDI Biotyper (Billerica, MA, USA) by following the manufacturer's instructions.

Antimicrobial susceptibility was evaluated by reference broth microdilution meth-

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TABLE 1 Antimicrobial susceptibility of 1,909 *Pseudomonas aeruginosa* clinical isolates from U.S. medical centers as part of the INFORM program in 2017

Antimicrobial agent by isolate group (*n*)	MIC_{50} (mg/liter)	MIC_{90} (mg/liter)	Susceptibility rates (%) according to[a]: CLSI S	CLSI R	EUCAST S	EUCAST R
All isolates (1,909)						
Ceftazidime-avibactam[b]	2	8	96.9	3.1	96.9	3.1
Ceftolozane-tazobactam[c]	0.5	2	97.5	1.3	97.5	2.5
Piperacillin-tazobactam	4	128	77.5	12.2	77.5	22.5
Ceftazidime	2	32	82.5	13.2	82.5	17.5
Cefepime	4	16	82.4	6.5	82.4	17.6
Meropenem	0.5	16	76.0	17.0	76.0	11.5
Doripenem	0.5	>8	77.4	16.6	69.4	22.6
Imipenem	1	>8	75.7	20.1	79.9	13.7
Aztreonam	8	>16	68.1	20.8	7.9	20.8
Ciprofloxacin	0.25	>4	77.9	16.2	70.8	29.2
Levofloxacin	1	16	72.1	18.9	61.3	38.7
Gentamicin	2	8	81.7	8.7	81.7	18.3
Amikacin	4	16	94.8	2.7	87.1	5.2
Tobramycin	0.5	2	93.1	5.3	93.1	6.9
Colistin	0.5	1	99.9	0.1	99.9	0.1
β-Lactam-nonsusceptible isolates (161)[d]						
Ceftazidime-avibactam[b]	8	32	70.2	29.8	70.2	29.8
Ceftolozane-tazobactam[c]	2	16	78.7	12.4	78.7	21.3
Aztreonam	>16	>16	2.5	88.2	0.0	88.2
Ciprofloxacin	4	>4	31.1	57.1	21.7	78.3
Levofloxacin	8	>16	23.1	65.6	11.2	88.8
Gentamicin	8	>16	48.4	31.1	48.4	51.6
Amikacin	8	>32	82.0	11.8	64.0	18.0
Tobramycin	2	>16	71.4	24.2	71.4	28.6
Colistin	0.5	1	100.0	0.0	100.0	0.0

[a]Resistance criteria as published by CLSI 2018 and EUCAST 2018. S, susceptible; R, resistant.
[b]Susceptible/resistant breakpoints of ≤8 and ≥16 mg/liter, respectively, for CLSI and EUCAST.
[c]Susceptible and resistant breakpoints of ≤4 and ≥8 mg/liter, respectively, for CLSI and EUCAST.
[d]Isolates nonsusceptible to ceftazidime, cefepime, meropenem, and piperacillin-tazobactam.

ods, conducted according to Clinical and Laboratory Standards Institute (CLSI) procedures (document M07) (10). Avibactam was provided by Allergan (Irvine, CA, USA) and combined with ceftazidime (avibactam at fixed concentration of 4 mg/liter) for susceptibility testing. A ceftolozane stock solution was obtained from Thermo Fisher Scientific (Cleveland, OH, USA) and combined with tazobactam (acquired from United States Pharmacopeia [USP]) at a fixed concentration of 4 mg/liter for susceptibility testing. All other compounds were obtained from USP or Sigma-Aldrich (St. Louis, MO, USA). Concurrent quality control (QC) testing was performed to ensure proper test conditions and procedures. QC strains included *Escherichia coli* ATCC 25922 and NCTC 13353, *Klebsiella pneumoniae* ATCC 700603 and ATCC BAA 1705, and *P. aeruginosa* ATCC 27853. CLSI and European Committee on Antimicrobial Susceptibility Testing (EUCAST) susceptibility interpretive criteria were used to determine susceptibility and resistance rates for comparator agents (11, 12).

Ceftazidime-avibactam (MIC_{50}/MIC_{90}, 2/8 mg/liter) and ceftolozane-tazobactam (MIC_{50}/MIC_{90}, 0.5/2 mg/liter) were the most active compounds after colistin, with national susceptibility rates of 96.9% and 97.5%, respectively (Table 1). Moreover, ceftazidime-avibactam and ceftolozane-tazobactam retained activity, 70.2% susceptibility and 78.7% susceptibility, respectively, against many isolates that were nonsusceptible to ceftazidime, cefepime, meropenem, and piperacillin-tazobactam (Table 1). Colistin (MIC_{50}/MIC_{90}, 0.5/1 mg/liter) was active against 99.9% of *P. aeruginosa* isolates overall (Table 1).

The aminoglycosides tobramycin (MIC_{50}/MIC_{90}, 0.5/2 mg/liter) and amikacin (MIC_{50}/MIC_{90}, 4/16 mg/liter) were also very active, demonstrating 93.1% susceptibility per CLSI and EUCAST and 94.8% and 84.1% susceptibility per CLSI and

EUCAST, respectively (Table 1). The national susceptibility rates for piperacillin-tazobactam (MIC_{50}/MIC_{90}, 4/128 mg/liter) and meropenem (MIC_{50}/MIC_{90}, 0.5/16 mg/liter) were 77.5% and 76.0%, respectively (CLSI and EUCAST), and ciprofloxacin was active against 77.9% and 70.8% of isolates per CLSI and EUCAST breakpoint criteria, respectively (Table 1). Of note, if the CLSI-revised breakpoints (to be published in January 2019) for ciprofloxacin ($\leq$0.5 mg/liter and $\geq$2 mg/liter for susceptible and resistant, respectively) and levofloxacin ($\leq$1 mg/liter and $\geq$4 mg/liter for susceptible and resistant, respectively) were applied, the susceptibility rates would be 70.8% for ciprofloxacin and 61.3% for levofloxacin.

After colistin, ceftazidime-avibactam and ceftolozane-tazobactam were the most active compounds in all census divisions and had susceptibility rates of 93.3% to 99.4% and 92.9% to 99.6%, respectively (Table 2 and Fig. 1). The highest susceptibility rates were observed in the East South Central division for ceftazidime-avibactam (99.4%) and in the West North Central division for ceftolozane-tazobactam (99.6%), whereas the lowest rates were observed in the Pacific division for both compounds, at 93.3% for ceftazidime-avibactam and 92.9% for ceftolozane-tazobactam (Table 2).

Susceptibility rates for other β-lactam compounds varied more broadly among the census divisions than with those of ceftazidime-avibactam and ceftolozane-tazobactam. The susceptibility rates for piperacillin-tazobactam ranged from 70.0% in the Mountain division to 85.4% in the West North Central division, and susceptibility rates to meropenem varied from 65.0% in the Middle Atlantic division to 84.2% in the West North Central division (Table 2).

Infections caused by MDR *P. aeruginosa* strains and a delay in appropriate antimicrobial therapy for serious *P. aeruginosa* infections are associated with increased mortality and longer hospital stays (2). Our results showed that in addition to colistin, only ceftazidime-avibactam and ceftolozane-tazobactam were active against $>$95% of the isolates overall. The susceptibility rates exhibited by these 2 combinations were generally very similar, with both being active against $>$90% of the isolates in all census divisions and retaining good activity against MDR isolates.

When the results from this investigation were compared with previous results obtained from the INFORM program (7, 8), we observed that the activity of ceftazidime-avibactam has remained stable since its initial U.S. FDA approval in early 2015 (97.0% susceptibility rate in the 2012 to 2015 period and 96.9% in 2017). In contrast, susceptibility rates have decreased for other β-lactams, such as those for meropenem (82.0% in 2012 to 2015 and 76.0% in 2017) and piperacillin-tazobactam (80.5% in 2012 to 2015 and 77.5% in 2017) (7, 8).

Resistance mechanisms related to ceftazidime-avibactam or ceftolozane-tazobactam were not evaluated in the present study, but the results from a previous investigation indicated that ceftazidime-avibactam-resistant isolates usually express more than 1 mechanism related to resistance to β-lactam compounds, including OprD loss, overexpression of chromosomal AmpC, and overexpression of MexCD-OprJ, MexAB-OprM, and/or MexXY-OprM (13). The study also showed that the resistance mechanisms found in ceftazidime-avibactam-resistant isolates were also found in ceftazidime-avibactam-susceptible isolates that were resistant to other β-lactams, and metallo-β-lactamase-producing *P. aeruginosa* isolates were rare in the U.S. medical centers that participate in the INFORM program (13). Additionally, it has been shown that resistance to ceftolozane-tazobactam is associated with alterations on the chromosomal AmpC Ω loop (14).

In summary, the results of this investigation corroborate and expand results from other investigations (7–9) and clearly show that the 2 novel cephalosporin–β-lactamase inhibitor combinations ceftazidime-avibactam and ceftolozane-tazobactam represent new alternatives with great potential to improve the outcomes of patients with *P. aeruginosa* infections, especially those caused by MDR strains.

TABLE 2 Antimicrobial susceptibility of 1,909 *Pseudomonas aeruginosa* clinical isolates stratified by U.S. census division in the INFORM program in 2017

Antimicrobial agent	% susceptible by U.S. census division (no. of isolates)								
	New England (157)	Middle Atlantic (334)	East North Central (342)	West North Central (240)	South Atlantic (219)	East South Central (156)	West South Central (156)	Mountain (80)	Pacific (225)
Ceftazidime-avibactam[a]	98.7	96.1	98.0	97.9	97.7	99.4	95.5	95.0	93.3
Ceftolozane-tazobactam[b]	97.5	97.6	98.0	99.6	98.6	98.7	98.1	96.2	92.9
Piperacillin-tazobactam	83.4	71.0	79.5	85.4	78.5	81.4	73.7	70.0	73.3
Ceftazidime	89.2	76.3	86.0	88.3	85.8	89.1	75.6	72.5	76.0
Cefepime	82.8	79.3	86.3	83.3	85.8	87.2	76.3	78.8	78.7
Meropenem	82.2	65.0	78.9	84.2	81.7	82.7	67.3	76.2	70.7
Ciprofloxacin	70.1	77.8	80.1	78.3	80.8	80.8	76.3	77.5	76.0
Levofloxacin	64.3	70.6	76.0	75.0	72.1	75.0	67.3	73.8	71.1
Amikacin	94.9	96.1	95.3	93.8	96.8	94.9	94.9	93.8	91.6
Tobramycin	89.8	93.7	93.3	95.0	96.8	92.9	90.4	90.0	92.0
Colistin	100.0	100.0	99.7	100.0	100.0	100.0	100.0	100.0	100.0

[a]Susceptible/resistant breakpoints of ≤8 and ≥16 mg/liter, respectively, for CLSI and EUCAST.
[b]Susceptible/resistant breakpoints of ≤4 and ≥8 mg/liter, respectively, for CLSI and EUCAST.

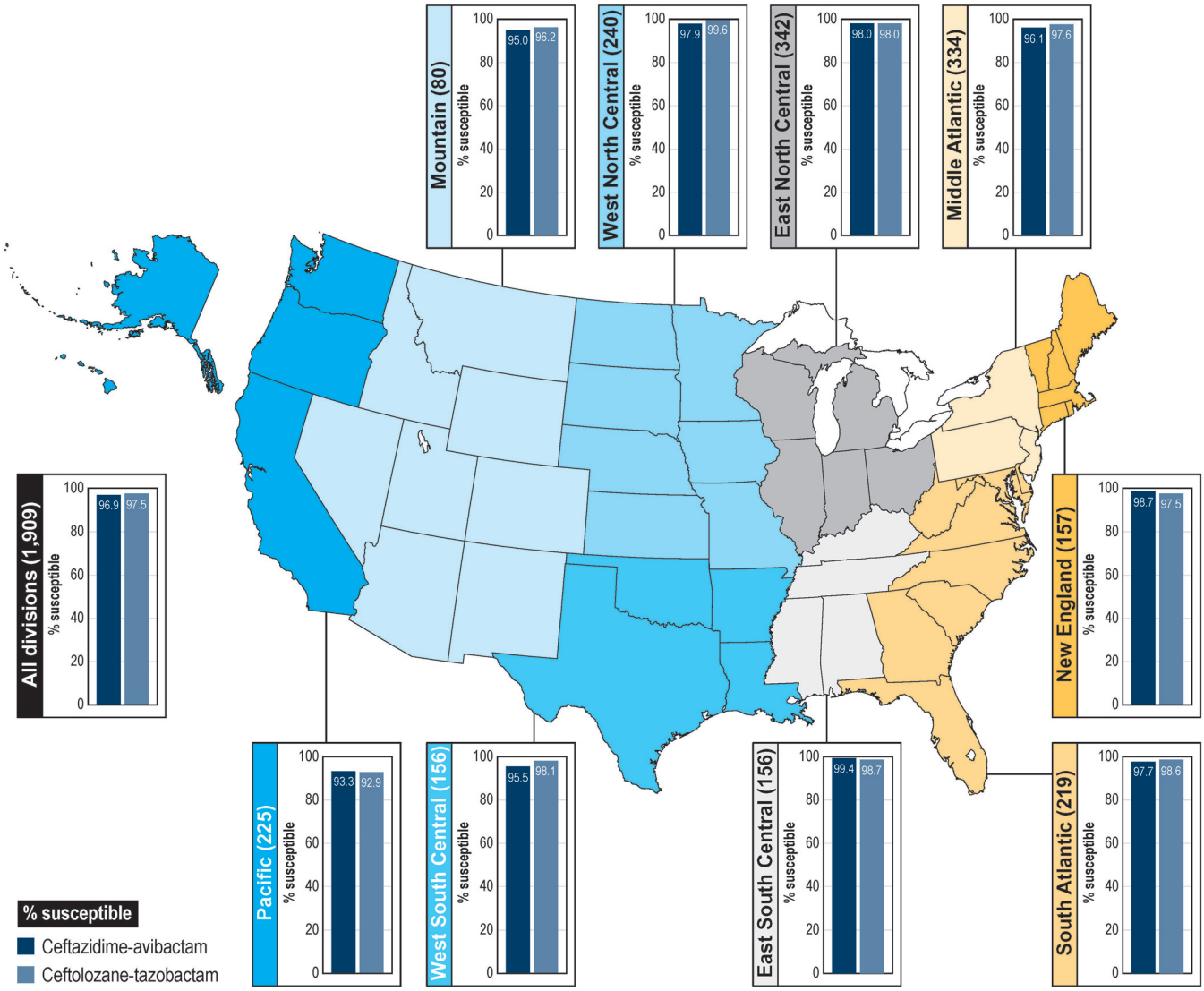

FIG 1 Susceptibility rates for ceftazidime-avibactam and ceftolozane-tazobactam stratified by census division.

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